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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/492,954	01/27/2000	Anna Marie Pyle	58077/JPW/JSG	1593

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EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/492,954	Pyle et al.
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Apr 10, 2003*.

2a) [X] This action is **FINAL**. 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-8* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-8* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [X] Other: *Detailed Action*

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1-5 and 7-8 are rejected under 35 U.S.C. 103 (a) over Shuman (Proc. Natl. Acad. Sci. USA, November 1992, Vol. 89, pages 10935-10939) in view of Bjornson et al. (Biochemistry, (1994), Vol. 33, pages 14306-14316).

Shuman teaches a method for detecting the release of a single-stranded RNA from an RNA duplex which comprise admixing an RNA helicase with the RNA duplex under conditions permitting the RNA duplex to unwind the RNA duplex and release single stranded RNA, wherein

the RNA duplex comprises a first RNA having a label and a second RNA wherein the unwound single-stranded RNA released from the duplex is detected by gel electrophoresis (Page 10936, Col. 1, lines 18-29, and 40-52, and Figures 1-2).

Shuman teaches a method, wherein ATP and a divalent cation is present (Methods Section, Enzyme Assays Subsection).

Shuman teaches a method of measuring the rate of release of a single-stranded RNA from an RNA duplex which comprises detecting whether the single-stranded RNA is released from the RNA duplex at predetermine time intervals, and determining therefrom the rate of release of the single-stranded RNA from the RNA duplex (Results Section, Kinetics Subsection and Figure 2).

Shuman teaches a method of determining whether a compound is capable of modulating the release of a single-stranded RNA from an RNA duplex (Results Section, Requirements of Helicase Activity Subsection).

Shuman does not teach the method, wherein the first label is capable of producing a luminescent energy pattern wherein the first RNA is present in the RNA duplex which differs from the luminescent energy pattern produced when the first RNA is not present in the RNA duplex, thereby detecting release of a single-stranded RNA from the RNA duplex.

Bjornson et al. teach the method, wherein the first label is capable of producing a luminescent energy pattern wherein the first nucleotide is present in the nucleic acid duplex which differs from the luminescent energy pattern produced when the first nucleotide is not present in the nucleotide duplex, thereby detecting release of a single-stranded nucleic acid from the nucleic

acid duplex after admixing helicase (Abstract, and Results section). Moreover, Bjornson et al. teach several advantages of using a fluorescent based assay for kinetic studies in general and particularly for mechanistic studies for helicase-catalyzed unwinding.

Shuman does not teach the method, wherein the first label is present at the 5' end of the first RNA and the second label is attached to the 3' end of the second RNA and the luminescent energy pattern results from interaction of luminescent energy released from the first label with the second label.

Bjornson et al. teach the method, wherein the first label is present at the 5' end of the first nucleic acid and the second label is attached to the 3' end of the second nucleic acid and the luminescent energy pattern results from interaction of luminescent energy released from the first label with the second label.(Materials and Methods Section, Preparation of DNA unwinding subsection, and Results section and Figure 1).

It would have been *prima facie* obvious to a practitioner having ordinary skill in the art at the time the invention was made to substitute and combine the method, wherein the first label is capable of producing a luminescent energy pattern wherein the first nucleotide is present in the nucleic acid duplex which differs from the luminescent energy pattern produced when the first nucleotide is not present in the nucleotide duplex, thereby detecting release of a single-stranded nucleic acid from the duplex after admixing helicase of Bjornson et al in the method of Schuman, since Bjornson et al. states, "We describe a fluorescence assay that can be used to monitor helicase-catalyzed unwinding of duplex DNA continuously in real time (Abstract, first sentence)."

Further motivation is provided by Bjornson et al. since Bjornson et al. states, "This emphasizes the utility of the continuous spectroscopic method described here, which allows many more time points to be collected, thus enabling more accurate determinations of the complete time course and observed rate constants for all phase of a multiphasic reaction (Page 14316, Column 1, last sentence of the second paragraph)." An ordinary artisan would have been motivated to substitute and combine the method, wherein the first label is capable of producing a luminescent energy pattern wherein the first nucleotide is present in the nucleic acid duplex which differs from the luminescent energy pattern produced when the first nucleotide is not present in the nucleotide duplex, thereby detecting release of a single-stranded nucleic acid from the duplex after admixing helicase of Bjornson et al in the method of Schuman, in order to achieve the express advantages, as noted by Bjornson et al., of a fluorescence assay that can be used to monitor helicase-catalyzed unwinding of duplex nucleic acids continuously in real time and which emphasizes the utility of the continuous spectroscopic method described here allowing many more time points to be collected, thus enabling more accurate determinations of the complete time course and observed rate constants for all phase of a multiphasic reaction.

3. Claim 6 is rejected under 35 U.S.C. 103 (a) over Shuman (Proc. Natl. Acad. Sci. USA, November 1992, Vol. 89, pages 10935-10939) in view of Bjornson et al. (Biochemistry, (1994), Vol. 33, pages 14306-14316) further in view of Vargo et al. (U.S. Patent 6,232,386 B1) (May 15, 2001).

Shuman in view of Bjornson et al teach the method of claims 1-5 and 7-8 as described above.

Shuman in view of Bjornson et al do not teach the labels fluorescein isothiocyanate and rhodamine isothiocyanate.

Vargo et al. teach the labels fluorescein isothiocyanate and rhodamine isothiocyanate (Column 29, lines 15-33).

It would have been *prima facie* obvious to a practitioner having ordinary skill in the art at the time the invention was made to substitute and combine the labels fluorescein isothiocyanate and rhodamine isothiocyanate of Vargo et al in the method of Schuman in view of Bjornson et al since Vargo et al states, "Oxyhalopolymer composites and surface-oxyhalogenated non-halopolymer composites that are refunctionalized with isothiocyanate substituted fluorophores are especially useful in a side variety of probes and sensors, such as for nucleic acids (Column 29, lines 29-33)." An ordinary artisan would have been motivated to substitute and combine the labels fluorescein isothiocyanate and rhodamine isothiocyanate of Vargo et al in the method of Schuman in view of Bjornson et al, in order to achieve the express advantages, as noted by Vargo et al., of oxyhalopolymer composites and surface-oxyhalogenated non-halopolymer composites that are refunctionalized with isothiocyanate substituted fluorophores especially useful in a side variety of probes and sensors, such as for nucleic acids.

Response to Arguments

4. Applicant's arguments filed on April 10, 2003 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually (Page 2, last paragraph to page 3, line 1) one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues (Page 3, first paragraph) that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Bjornson et al as Bjornson et al state, "This is especially advantageous for studies of multiphasic time courses since a spectroscopic assay enables many data points to be obtained within each phase of the reaction, whereas this requires multiple experiments using a discontinuous assay. The several hundred data points obtained for each unwinding trace also enables more accurate determination of the observed kinetic parameters (page 14314, Column 1, lines 27-33)". Similar motivation is provided by new reference Vargo et al.

Applicant also argues (Page 2, lines 6-11) that the 103 rejection is improper because it lacks a reasonable expectation of success.

With regard to the "lacks a reasonable expectation of success" argument, The MPEP 2143.02 states,"Obviousness does not require absolute predictability, however, at least some

degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. The applicant did not provide any evidence or reason that fluorescence labeled probes of Bjornson would be non-functional with RNA helicase enzyme of Shuman. There is evidence in the Bjornson reference of the enabling methodology, the suggestion

to modify the prior art, and evidence that a number of different dyes were actually experimentally studied and found to be functional to monitor the helicase activity (Abstract). This evidence of functionality trumps the attorney arguments, which argues that Bjornson reference is an invitation to research, since Bjornson steps beyond research and shows the functional product.

Applicant also argues (Page 4, third paragraph) that Vargo reference has a motivation which is different from the applicant's motivation. This argument is not persuasive. In response to applicant's argument, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In response to argument, all the previous 103(a) rejections are hereby properly maintained.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located In Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published In the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti

Patent Examiner

Art Unit 1634

May 7, 2003

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